Available online on 15.03.2023 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

Open Access to Medical Science and Pharma Research

Open Access **Review Article**

An Updated Review on Recent Advancements in the Diverse Biological Applications of Medicinally Privileged Scaffold: Chalcone and its derivatives

Praveen Sekar, Shridharshini Kumar, Senthil Kumar Raju*

Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode – 637 205, Tamilnadu, India

Article Info:

Article History:

Received 07 Jan 2023
Reviewed 21 February 2023
Accepted 03 March 2023
Published 15 March 2023

Cite this article as:

Sekar P, Kumar S, Raju SK, An Updated Review on Recent Advancements in the Diverse Biological Applications of Medicinally Privileged Scaffold: Chalcone and its derivatives, International Journal of Medical Sciences & Pharma Research, 2023; 9(1):7-20

DOI: http://dx.doi.org/10.22270/ijmspr.v9i1.61

*Address for Correspondence:

Dr. R. Senthil Kumar, Professor & Head, Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamilnadu, India

Abstract

Fused heterocyclic compounds rank among the most significant systems in medicinal chemistry because of their wide-ranging biological effects. Among the various class of compounds, chalcones and their derivatives are found to be one of the important classes in the field of synthetic and pharmaceutical chemistry. These derivatives are mainly synthesized by means of Claisen-Schmidt condensation, Crossed Aldol condensation and Knoevenagel condensation reactions, which provides wider applications in the field of medicine. Due to the broader biological applications like antimicrobial, anticancer, antimalarial, antioxidant, anti-inflammatory, antitubercular, antidiabetic, antileishmanial, anti-vitiligo and neuroprotective properties, these derivatives extended their role in coordination chemistry and also act as intermediates for the synthesis of various organic derivatives containing isoxazole, pyrazole, pyrimidine, naphthalene, indole, polyamine and other moieties as hybrid molecules. The present review discusses the biological applications of various chalcone derivatives. Due to their easiest way of synthesis, nowadays, these types of derivatives were tried for various ailments and by means of implementing various greener chemistry approaches, novel and potent derivatives can be synthesized and applied for various applications. Thus, this review will be helpful for the design of potent chalcone derivatives for numerous applications in the future.

Keywords: Chalcones, 1,3-diphenyl-2-propene-1-one, microbial properties, anticancer, antioxidant, neuroprotective and biological applications

Introduction

The term "heterocyclic compound" refers to organic molecules that have at least one carbon atom with at least one other heteroatom, such as an N, O or S atom. For the metabolism of biological cells, they are essential. They often have five or six members and some of their rings have compositions that are greater than those of rings with three, four, seven or more members. Heterocyclic chemistry has drawn significant interest in the pharmaceutical and synthetic organic chemistry because of the wide range of pharmacological and therapeutic implications[1]. One of the most significant groups of heterocyclic molecules with extensive medicinal applications is chalcones, which can be produced synthetically or naturally as flavonoids. Chemically speaking, the chalcone is composed of polyphenolic molecules from the flavonoid family called 1,3-diphenyl-2-propene-1-one. The chalcones are open-chained molecules with two aromatic rings that are connected by three carbon chains that each include a carbonyl group and an α,β-unsaturated bond[2-4]. Moreover, these substances can be found in naturally occurring products like plant allelochemicals and insect hormones. Chalcones undergo a wide range of chemical reactions in addition to being used to make heterocyclic compounds. It is possible to create a wide range of chalcone derivatives by combining aromatic aldehydes with aryl ketones by utilizing the proper amount of condensing agents. Chalcones serve as the initial intermediate structure in the synthesis of flavonoids, isoflavonoids and aurones in many biosynthetic pathways[5]. Chalcone has two aromatic rings with p-electron systems and conjugated double bonds with absolute delocalization, giving them a relatively low redox potential and a higher likelihood of undergoing electron transfer processes[6].

Similar to chalcones, coumarins, hydroxy coumarins, chalconoids and curcuminoids are naturally occurring moieties with an, -unsaturated carbonyl system, extending their potential towards cancer. For example, the compounds containing hydrazide-hydrazone, acrylonitrile, and 2-amino-3-cyanopyridine moieties displayed significant anticancer potential[7]. The chalcones and their derivatives were made using a variety of synthetic techniques, such as base-catalysed condensation reaction[8], Claisen-Schmidt condensation[9], Knoevenagel condensation[10], microwave- and ultrasonic-assisted synthesis[11,12], refluxing[13], stirring at high temperature[14] and molecular hybridization[15]. The Claisen-Schmidt condensation method was by far the most effective in synthesizing chalcones and their derivatives.

These chalcones and their derivatives have been reported to exhibit a wide variety of therapeutic and pharmacological applications including anticancer[16], antimicrobial[17], antitubercular[18], antioxidant[19], anti-inflammatory[20], larvicidal[21], antiplasmodial[22], neuroprotective[23], cholinesterase inhibitors[24], antidepressant[25], anti-diabetic[26] and vitiligo treatment[27]. Among these therapeutic uses, chalcones and their derivatives have focused more on cancer since they can control tumor neo-angiogenesis and have improved anticancer potential by blocking many signaling pathways while having low toxicity to normal cells[28,29].

In this review, only the literature indexed in Scopus, PubMed, Google Scholar, Embase, ResearchGate and Web of Science databases were collected by using the keywords such as chalcones, diphenyl propene-1-ones, Claisen-Schmidt condensation, antimicrobial, anticancer, antioxidant, anti-inflammatory, antitubercular and therapeutic applications, individually and in combination between the time period of 2016 to 2023. Here, we summarized the various biological applications of novel and efficient chalcones and their derivatives.

Antimicrobial activity of chalcones and their derivatives

Antibiotic-resistant organisms have a negative impact on the effectiveness of antibiotics, despite the fact that they are considered one of the most effective therapies in medicine. (E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4-((1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one **(1)** was synthesized by irradiation of propargylated chalcone with 4-methoxy phenacyl azide under microwave conditions. The compound was evaluated for its antimicrobial activity and was found to be active against *Staphylococcus aureus*, determined by the inhibition of biofilm formation[17]. (E)-1-(3′-aminophenyl)-3-(4-bromophenyl)prop-2-en-1-one **(2)** was synthesized and evaluated its antimicrobial efficacy, found to be highly active against *S. aureus*[30]. Azulene-containing chalcone, (E)-1,3-Di(azulen-1-yl)prop-2-en-1-one **(3)** was prepared by the reaction between 1-azulenecarbaldehyde and ketone in ethanol. The antimicrobial efficacy of the synthesized compound was evaluated and found to be active against the fungal strain, *Candida parapsilosis*[31]. Novel (E)-1-(aryl)-3-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl) prop-2-en-1-ones **(4,5)** were synthesized and evaluated its potential against *Aspergillus spp*. using broth microdilution method. Both of these compounds were found to be highly active and possessed fungicidal activity[32]. (2E)-1,3-diphenyl prop-2-en-1-one **(6)** and (2E)-3-[4-(dimethylamino)phenyl] -1-phenyl- prop-2-en-1-one **(7)** were synthesized by the reaction of 1-(2,2-Dimethylchroman-6-yl)ethanone with substituted benzaldehydes under stirring conditions. The antifungal activity of the synthesized compounds was tested against *Botrytis cinerea* and *Monilinia fructicola* using an *in vitro* radical growth rate assay. Compound **(6)** was active against *B. cinerea* and compound **(7)** was found to be active against *M. fructicola*. Similarly, the compound **(8)**, (2E)-3-(benzo[d] [1,3]dioxol-5-yl)-1-(2,2-dimethyl-chroman-6-yl)prop-2-en- 1-one, the dihydrochromane–chalcone hybrid was also found to be a potent antifungal agent. I.e., effective against *M. fructicola*[33].

Based on the Claisen-Schmidt condensation, the two novel chalcones namely, (2E)-1-(4′ -aminophenyl)-3-(phenyl)-prop-2-en-1-one **(9)**, and (2E)-1-(4′-aminophenyl)-3-(4-chlorophenyl)-prop-2-en-1-one **(10)** was designed and prepared by the condensation of p-aminoacetophenone and benzaldehyde with ethanol. The designed compounds were subjected to evaluate the antibacterial efficacy against different microorganisms and found to be highly effective against *S. aureus*. Compound **(9)** exhibited synergistic activity with the standard compound, gentamycin, while compound **(10)** was non-synergistic with it. The reason for the loss of synergistic activity was due to the presence of the halogen substituents[34]. Fluorinated chalcone-1,2,3-triazole conjugates were designed and synthesized by Yadav et al., 2018. The antimicrobial potential of the designed compounds was tested against both gram-positive (*S. epidermidis* and *Bacillus subtilis*), gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) microorganisms and antifungal (*A. niger* and *C. albicans*) microorganisms. Among the designed compounds, the compound, (E)-1-(4-bromophenyl)-3-(2-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)prop-2-en-1-one **(11)** was found be active against the fungal strain, *C. albicans*. The compound, (E)-3-(2-((4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-methoxy phenyl)prop-2-en-1-one **(12)** was found to be active against both *A. niger* and *C. albicans*. On focussing towards antibacterial, the compound, (E)-3-(2-((1-(4-fluorobenzyl-1H-1,2,3-triazol-4-yl)methoxy)naphthalene-1-yl)-1-(4-nitro phenyl)prop-2-en-1-one **(13)** was highly effective against *P. aeruginosa*[35].

Fluoro-substituted chalcones were synthesized and evaluated their efficiency as antimicrobial agents. The compound (2E)-3-phenyl-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one **(14)** and (2E)-3-(2-fluorophenyl)-1-(2,4,6-trimethoxyphenyl)prop-2-en-1-one **(15)** was found to be effective against the tested fungal strains, *C. albicans*, *C. glabrata*, and *C. parapsilosis* and the compound **(14)** also exhibited better bactericidal activity against *S. aureus*, *S. pyogenes*, *Enterococcus faecalis*, *E. coli* and *P. aeruginosa* bacterial strains[36]. The thiazole-based chalcones were designed, synthesized and the antibacterial potential was evaluated by Alrohily et al., 2019. Among the various derivatives, the compound (E)-9-)(4-methoxybenzylidene)-5-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-thiaolo[2,3-b]quinazoline **(16)** was found to be highly effective against both gram-positive and gram-negative bacterial species, *S. aureus* and *Micrococcus luteus*, determined by the antibiofilm activity[37].

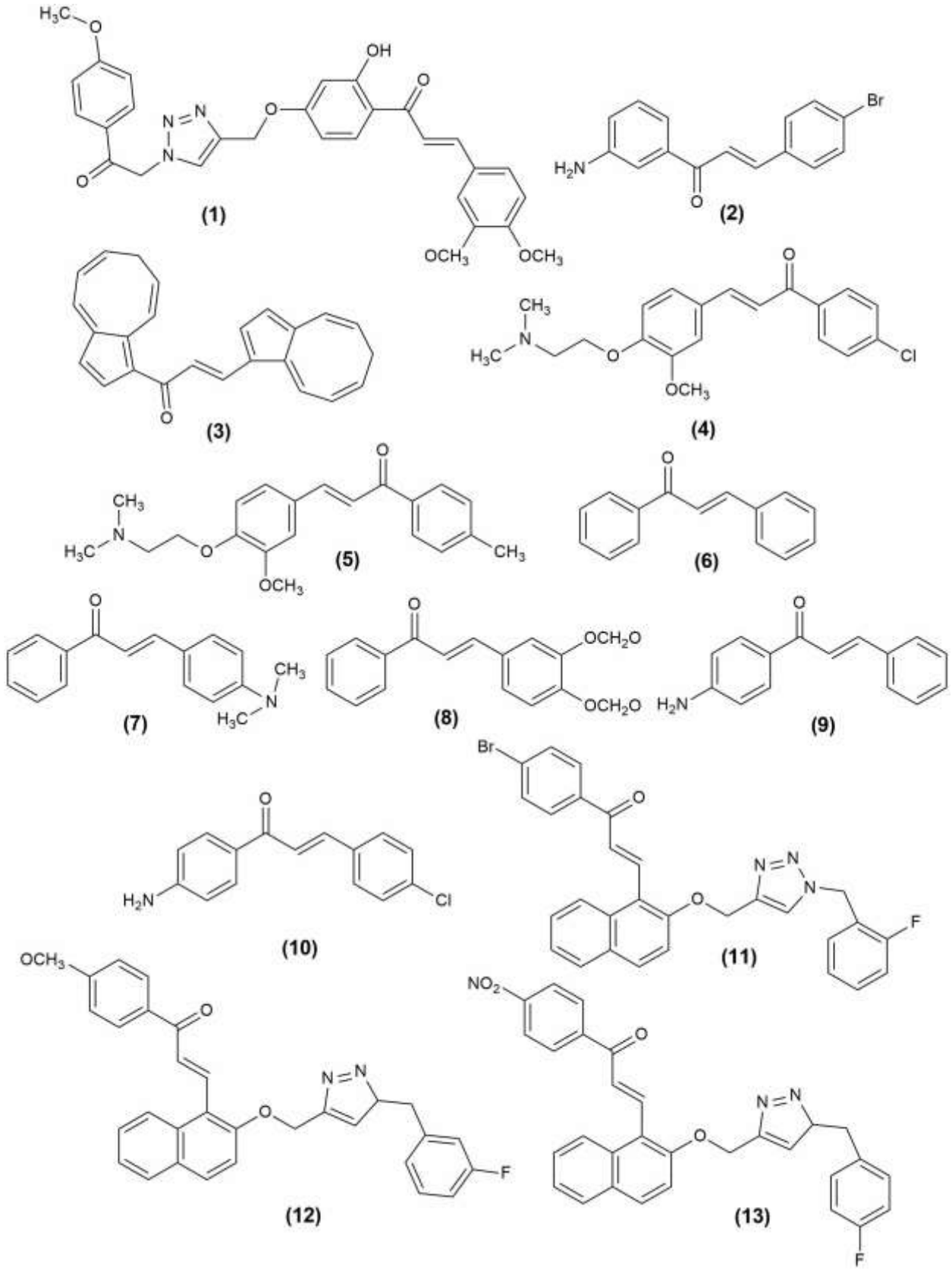

Figure 1: Compounds possessing antimicrobial activity

Antitubercular activity of chalcones and their derivatives

Chalcone-sulphonamide hybrids **(17,18)** were synthesized by the reaction between various sulphonamide derivatives and aromatic aldehydes by the Claisen-Schmidt condensation reaction. The obtained chalcone hybrids were tested against the *Mycobacterium tuberculosis* H37Rv strain to determine the antitubercular efficiency of the compounds. The compounds (E)-N'-Isonicotinoyl-2,4-dimethoxy-5-(3-(3,4,5-trimethoxyphenyl)acryloyl) benzenesulfonohydrazide **(17)** and (E)-5-(3-(Benzo[d][1,3]dioxol-5-yl)acryloyl)-N'-isonicotinoyl-2,4-dimethoxybenzenesulfonohydrazide **(18)** were found to be highly effective antitubercular compounds[18]. Pyrazole–coumarin and pyrazole–quinoline chalcones were synthesized by the reaction of pyrazole carbaldehyde and 3-

acetyl coumarin/ substituted 1- (2-methyl-4-phenylquinolin-3-yl)ethanone in the presence of piperidine, respectively and evaluated their potency as antitubercular agents against *M. tuberculosis* H37Rv strain using the MABA (microplate Alamar Blue assay) method. The synthesized coumarin derivative, 7-Methoxy-3-[(2E)-3-[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-4- yl]-prop-2-enoyl] -2H-chromen-2-one **(19)** and quinoline derivative, (2E)-3-[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]-1-[6-c hloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl]prop-2-en-1-one **(20)** was found to be potent compounds against the tested organism with better MIC values. The in silico molecular docking studies also revealed and confirmed that these compounds were highly active against the tubercular species[38].

Uracil-ferrocenyl chalcone conjugates **(21,22)** were synthesized by the reaction of O-propargylated ferrocenyl chalcone with N-alkylated-azido-uracil under continuous stirring for 10-11 h and evaluated their potential against *M. tuberculosis* mc²6230 strain. Both of the compounds were active against the tested strain but were found to be a loss of activity than their non-chalcone hybrids[39]. Chalcone based on nitro thiophene analogue, (2E)-1-[4-(1H-imidazol-1-yl)phenyl]-3-(5-nitrothiofen-2-yl)prop-2-en-1-one **(23)** was evaluated against *M. tuberculosis* H37Rv strain to determine its antitubercular potential using the MABA (Microplate Alamar Blue Assay) method and found to be a potent compound for tuberculosis, which was due to the presence of nitro thiophene moiety in its structure. i.e., it showed 5.5-fold increase in the activity[40].

The chalcone linked 5-phenyl-3-isoxazole carboxylic acid methyl ester derivative, Methyl-(E)-5-(3-(4-(3-oxo-3-(4-propoxyphenyl)prop-1-en-1-yl)benzamido)phenyl)isoxazole-3-carboxylate **(24)** was obtained by the condensation of Methyl 5-(3-aminophenyl)isoxazole-3-carboxylate with carbonic acid derivative. The antitubercular potential of the compound was evaluated against drug-resistant *M. tuberculosis* and found to be highly potent against *M. tuberculosis* H37Rv strain with better MIC value[41].

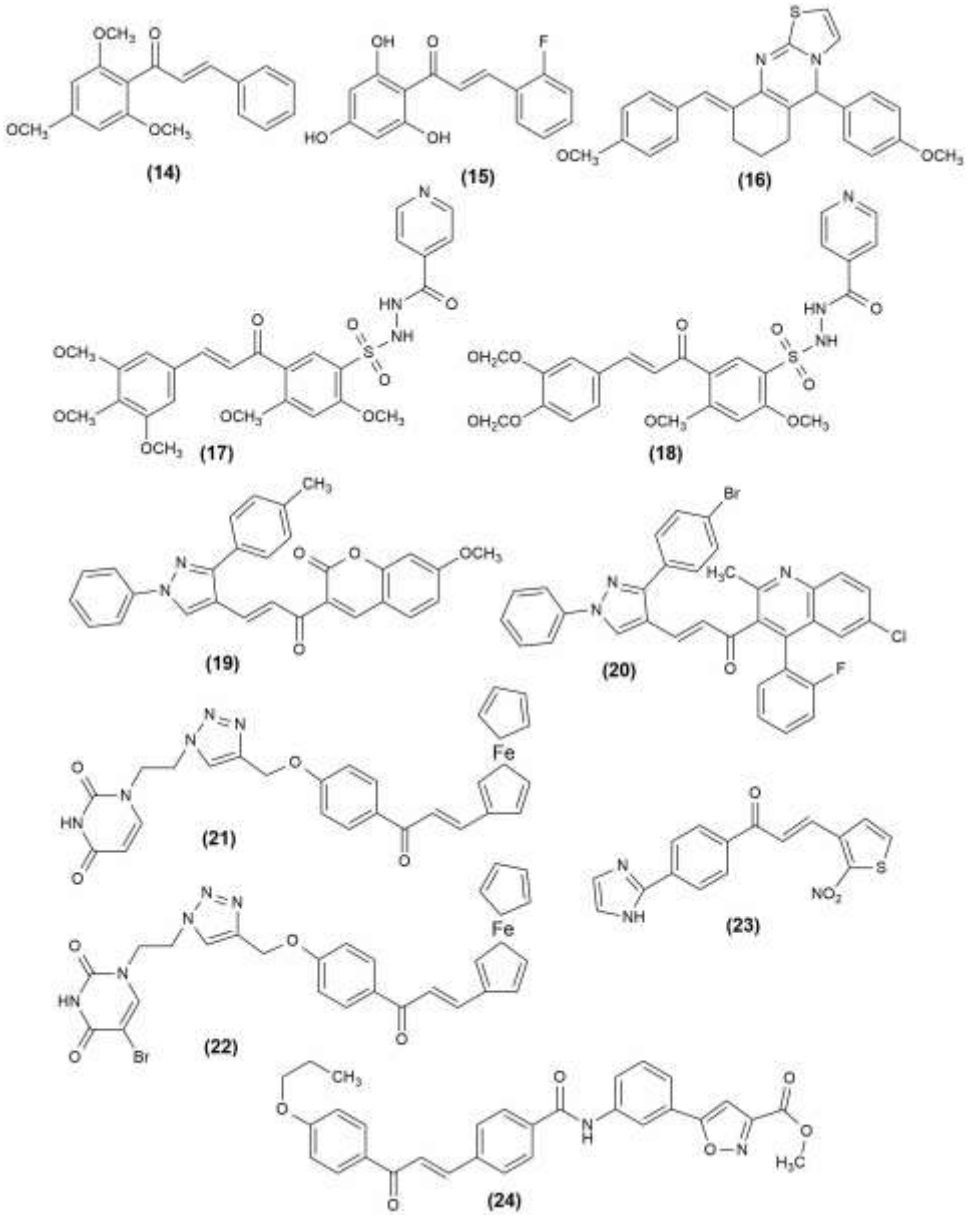

Figure 2: Compound possessing antimicrobial (14-16) and antitubercular (17-24) activities

Antimalarial activity of chalcones and their derivatives

4-aminoquinoline-chalcone/ferrocenyl-chalcone conjugates **(25,26)** were prepared and reported by Singh et al., 2017. The aldol condensed product of o-bromoalkyl acetophenone with 7-chloro-4-piperazine-quinoline and substituted aryl aldehyde/ ferrocene-carboxaldehyde resulted in the formation of corresponding 4-aminoquinoline-chalcone/ ferrocenyl-chalcone hybrids was obtained, respectively. These compounds were found to be effective against chloroquine-resistant and mefloquine-sensitive W2 strain of *Plasmodium falciparum* with better IC_{50} values[22]. The antimalarial potential of the quinolinyl chalcone **(27)** was evaluated against chloroquine (CQ) sensitive and resistance (CQ- resistance) strain of *P. falciparum* and found to be a potent compound, which was due to the presence of bromine substituent. The molecular docking studies also revealed that this compound was found to be having a better binding affinity with significant activity[42].

(E)-3-(3,4-dihydroxyphenyl)-1-(2-hydroxy-4-methoxyphenyl) prop-2-en-1-one **(28)** was synthesized by the Claisen-Schmidt condensation of substituted benzaldehyde with substituted acetophenone. The antimalarial potency of the compound was evaluated against chloroquine-sensitive *P. falciparum* 3D7 strain and possessed excellent activity with a better IC_{50} value. The molecular docking studies also revealed that the compound was highly active against the dihydrofolate reductases–thymidylate synthase (PfDHFR-TS) protein[43]. Aminoalkylated chalcone derivative, (E)-1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxy-5-(piperidin-1- ylmethyl)phenyl)-prop-2-en-1-one **(29)** was obtained by the reaction of chalcone afforded from vanillin and chloroacetophenone with formaldehyde and piperidine under stirring conditions. The resulted chalcone-based mannich base derivative **(29)** was found to be active against chloroquine-sensitive *P. falciparum* 3D7 strain, determined by both in vitro and in silico molecular docking experiments[44].

Indolyl-chalcone hybrid, Trans-3-(1H-indol-3- yl)-1-(2'-hydroxyphenyl)-2-propen-1-one **(30)** was also exhibited against *P. falciparum*, NF54 strain. The better activity of this compound was due to the presence of the hydroxyl substituent at the second position of the phenyl group, which exhibited better IC_{50} value[45]. (E)-1-(4-Chlorophenyl)-3-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one was treated with propargyl bromide, afforded (E)-1-(4-Chlorophenyl)-3-(4-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)-3- methoxyphenyl)prop-2-en-1-one **(31)**. The obtained compound was tested and found to be effective against chloroquine-sensitive *P. falciparum* 3D7 (Pf3D7) strain and chloroquine-resistant *P. falciparum* K1 strain, determined by using SYBR-Green-I assay[46]. The antimalarial activity of the compound (2E)-3-(3,4-dimethoxyphenyl)-1-(3,4,5-trimethoxycyclohexa-1,3-diene-1-yl)prop-2-en-1-one **(32)** was evaluated using WHO Mark III schizont maturation inhibition assay and found to be active against chloroquine-resistant *P. falciparum* strain[47].

Anticancer activity of chalcones and their derivatives

A novel chalcone-polyamine conjugate, Synthesis of 4-[N1 -spermidine-3-aminopropyloxy]-3',4',5' – trimethoxychalcone **(33)** was obtained by coupling the bromide group of 4-bromopropyloxy-3',4',5' – trimethoxy chalcone with primary amine function of polyamine by means of nucleophilic substitution reaction. The antiproliferative activity of the compound was tested against human colorectal (HT-29 and HCT116) and prostate (PC3 and DU145) cancer cell lines using an MTT assay. The tested compound was found to be highly effective against the tested cell lines and found to be blocking the G1 and G2 phase cell cycle, thus induced apoptosis[3]. (E)-4-chloro-N-(4-(3-oxo-3-(3,4,5-trimethoxyphenyl) prop-1-en-1-yl) phenyl) butanamide **(34)** was synthesized and evaluated against MGC-803 (gastric), HCT116 (colon) and MCF-7 (breast) cancer cell lines using an MTT assay.

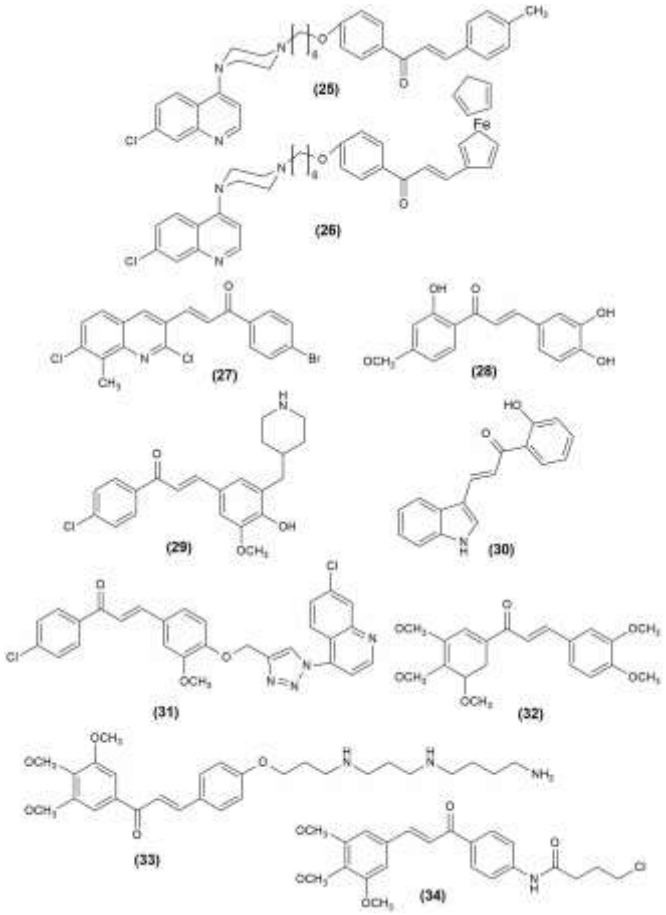

Figure 3: Compounds possessing antimalarial (25-32) and anticancer (33-34) activities

The tested compound was found to be active against the tested cell lines and also found to be inducing apoptosis, determined by the western blot analysis and flow cytometry[4]. The benzo[d]imidazo[2,1-b]thiazole-chalcone conjugates **(35,36)** exhibited better anticancer effects against the breast cancer cell line, MDA-MB-231 with better IC_{50} values. It was found to be inducing apoptosis, determined by annexin V-FITC/PI assay and the flow cytometry revealed that this compound arrested the cell cycle at the G2/M phase[16].

The breast cancer activity of the synthesized derivative, (8S,9S,10R,13S,14S,17S)-17-[(2E)-3-(4-fluorophenyl)prop-2-enoyl]-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15-decahydro cyclopenta[a]phenanthren-3-one **(37)** was determined by the MTT assay. The compound was found to be active against two breast cancer cell lines namely, MCF-7 and MDA-MB-231 with better IC_{50} values[28]. Chalcone containing naphthalene moiety namely, (E)-3-(4-(Diethylamino)phenyl)-1-(4-methoxy naphthalen-1-yl)prop-2-en-1-one **(38)** was screened against HCT116 (colorectal) and HepG2 (liver) cancer cell lines and found to be highly effective against both of the cell lines. Furthermore, the tested compound induced cell cycle arresting at the G2/M phase and the molecular docking results revealed that this compound exhibited significant binding interaction with the colchicine site of tubulin[48]. The other

derivative of the same class, (E)-3-(3-Hydroxy-4-methoxyphenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one **(39)** was also found to be possessing significant anticancer activity against MCF-7 breast cancer cell line, followed by cell cycles arresting at G2/M phase[49]. Similarly, the chalcone containing indole and naphthalene moieties **(40)** was also found to be novel tubulin polymerization inhibitors and active against liver, colon and breast cancer cells[50].

Chalcone containing thieno[2,3-d]pyrimidin-2-yl derivative, (E)-2-(3-(2,4,6-Trimethoxyphenyl)-3-oxoprop-1-en-1-yl)-6-methylthieno[2,3-d]pyrimidin-4(3H)-one **(41)** was active against colon cancer cell line and induced apoptosis through the mitochondrial cell death pathway and induced PARP-1, caspase cleavages[51]. The cytotoxic potential of 6'-benzyloxy-4-bromo-2'-hydroxychalcone **(42)** was evaluated against a panel of cancer cell lines and found to be effective against U937, HL-60, NALM-6, MOLT-3 leukaemia cell lines. This compound induced apoptosis by generating reactive oxygen species through the mitochondrial pathway[52]. The in vitro antiproliferative activity of the compound, (E)-1-(4-Amino-2-(pyrrolidin-1-yl)thiazol-5-yl)-3-(2,4-dichlorophenyl)prop-2-en-1-one **(43)** was evaluated and found to be effective against MCF-7 (breast), HepG2 (liver) and SW480 (colorectal) cancer cell lines. It also induced apoptosis by inducing the G2 phase cell cycle arresting[53].

(E)-1–(1-Hydroxy-4,5,8-trimethoxynaphthalen-2-yl)-3-(quinolin-6-yl) prop-2-en-1-one **(44)** was synthesized and found to be effective against gastric cancer cell lines (HGC27, MKN28, AZ521, AGS, and MKN1). This compound was also found to be an apoptosis-inducing agent, thus suppressed STAT3 phosphorylation[54]. Novel halogenated phenoxy chalcone, 3–(4-(4-Bromophenoxy)phenyl)-1-(p-tolyl)prop-2-en-1-one **(45)** was evaluated and found to be active against MCF-7 breast cancer cell line using an MTT assay. It also suppressed mitogen-activated protein kinase, followed by inducing apoptosis through the blockade of the G2/M phase cell cycle[55]. 3-(4-Methoxyphenyl)-1-(5-methyl-2-(methylamino)thiazol-4-yl)prop-2-en-1-one **(46)** was found to be exhibit broad antitumor activity and induced apoptosis by inhibiting G2/M phase cell cycle[56]. The antiproliferative compound, 3-Aminomethyl pyridine chalcone derivative **(47)** with apoptosis-inducing capability exhibited better activity against various cancer cell lines[57].

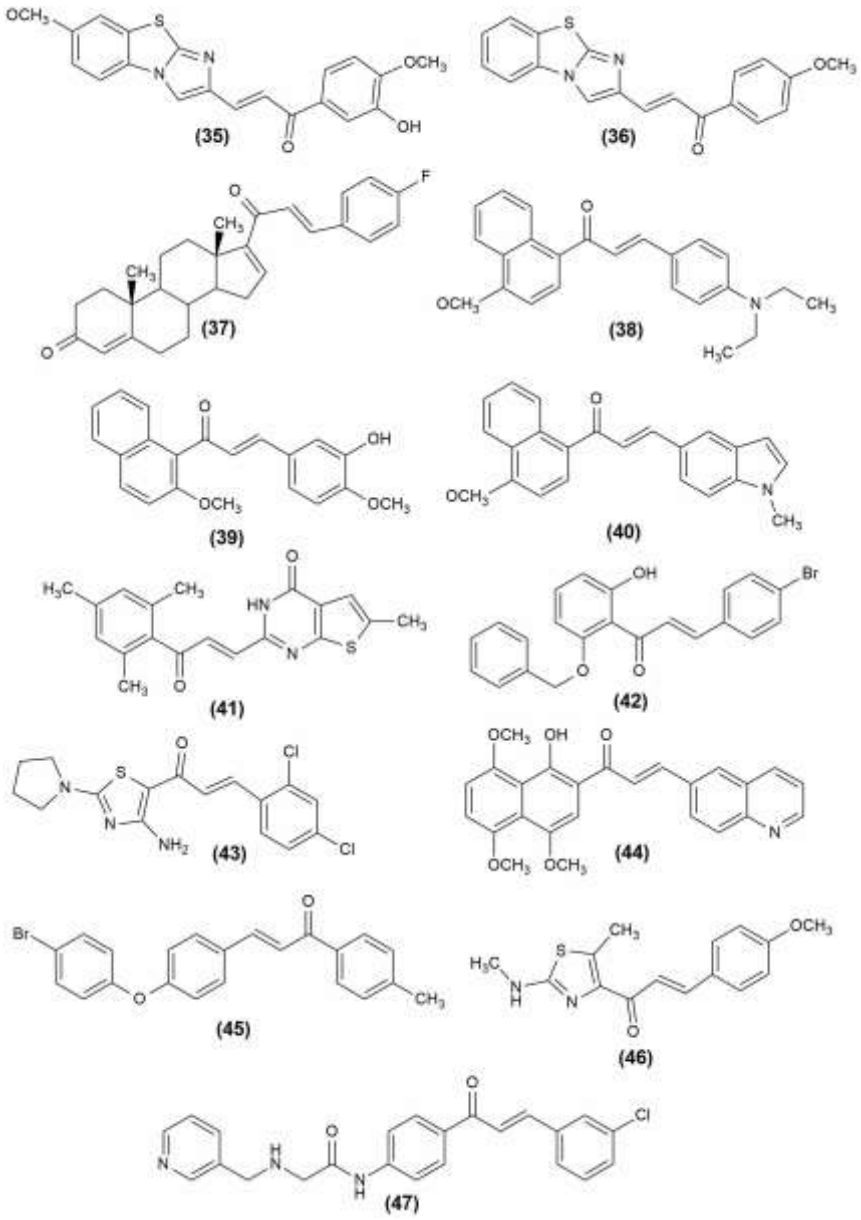

Figure 4: Compounds possessing anticancer activity

The xanthine oxidase inhibitory and antiproliferative activity of the derivatives, (2E,2'E)-1,1'-(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis(3-(2,5-difluorophenyl)prop-2-en-1-one) **(48)** and (2E,2'E)-1,1'-(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis(3-(3,4- difluorophenyl)prop-2-en-1-one) **(49)** were evaluated and found to be possessing significant activity against cancer cell lines. The molecular docking analysis revealed that this compound successfully inhibited the xanthine oxidase[58]. Novel Chalcone-1,2,3-triazole-azole derivate, (E)-1-(4-(3-(4-(((1,3,4-Thiadiazol-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)propoxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(50)** was synthesized and evaluated against SK-N-SH (glioblastoma), EC-109 (oesophageal) and MGC-803 (gastric) cell lines. The compound was found to be active against SK-N-SH cell line with a better IC_{50} value[59]. Novel ligustrazine-chalcone derivative **(51)** was found to be active against triple-negative breast cancer and induced apoptosis through the cell cycle arresting at G0/G1 phase[60]. Chalcone incorporated quinazoline derivatives were designed and evaluated against various cancer cell lines and the compound, (E)-1-(2-Fluoro-4-(trifluoromethyl)phenyl)- 3-(4-(quinazolin-4-ylamino)phenyl)prop-2-en-1-one **(52)** was found to be effective against A549 (lung), HT-29 (colorectal), MCF-7 (breast) and A375 (skin) cancer cell lines[61].

Novel Benzimidazole-Pyrazoline Hybrid Molecule containing chalcone derivative, Ethyl 2-(2-cinnamoyl-1H-benzo [d]imidazol-1-yl)acetate **(53)** also exhibited significant anticancer activity against the breast cancer cell line, MDA-MB-231 with a better IC_{50} value[62]. The anticancer potential of the compound, (E)-1-(4-(3-chlorocyclopenta-1,3-dien-1-yl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one **(54)** was evaluated by an *in silico* experiment, using epidermal growth factor receptor as target and found to be more potent than doxorubicin for hepatocellular carcinoma[63]. The anticancer and apoptotic potential of the compound, 1-(4-(4-(2-Methoxyethyl) piperazin-1-yl)phenyl)- 3-(naphthalen-2-yl)prop-2-en-1-one **(55)** was evaluated against A549 lung cancer cell line using an MTT assay. It was found to be highly active and exhibited significant apoptosis, determined by the flow cytometry analysis. The molecular docking studies against vascular endothelial growth factor receptor-2 and caspase enzymes exhibited better binding energy, which revealed that this compound was an anticancer agent with significant binding interactions[64].

Antioxidant activity of chalcones and their derivatives

Bis-Chalcones **(56,57)** were synthesized by using the Claisen-Schmidt condensation reaction and the free radical scavenging potential of these compounds was evaluated using FRAP assay. These compounds exhibited better activity with significant EC_{50} values, which was due to the presence of chlorine substitution in the aromatic ring[21]. Hesperidin methyl chalcone **(58)** increased the production of reactive oxygen species and showed significant antioxidant activity, determined by the FRAP and ABTS radical scavenging activity[65].

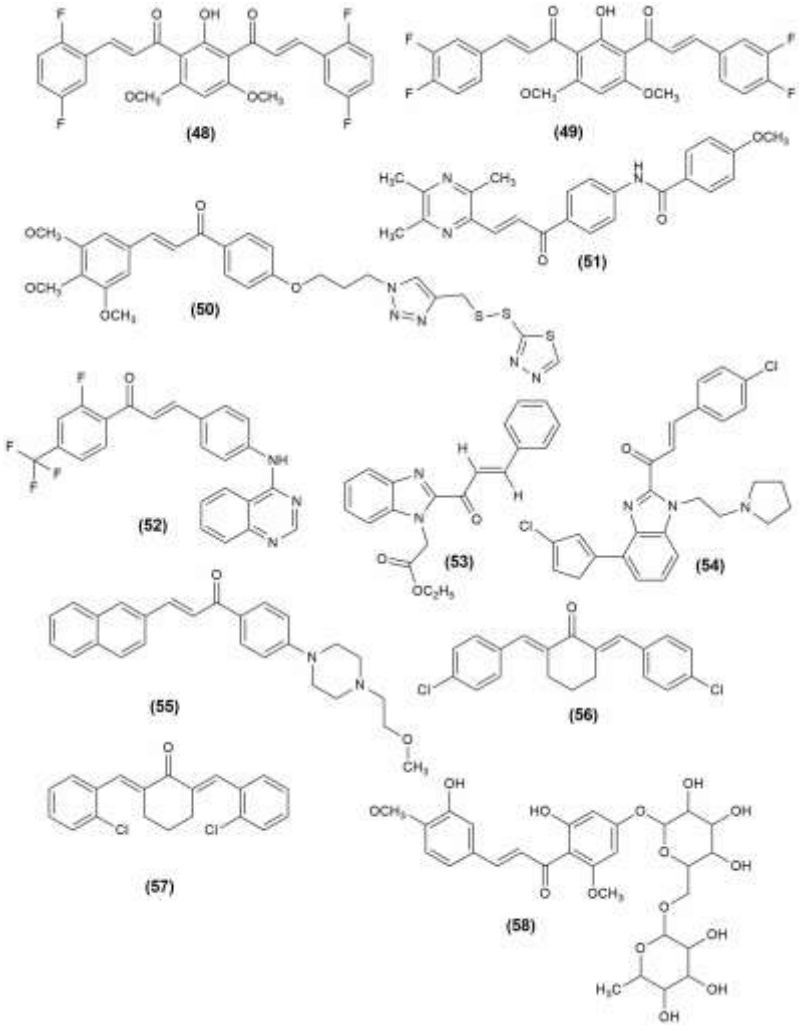

Figure 5: Compounds possessing anticancer (48-55) and antioxidant (56-58) activities

The *in vitro* antioxidant potential of the coumarin clubbed chalcone hybrid **(59)** was evaluated by using DPPH free radical scavenging method. The evaluated compound was found to be having greater antioxidant potential, due to the presence of electron releasing 2- OH group in its structure[66]. Alkyl-substituted pyrazine derivative of chalcone **(60)** exhibited significant radical scavenging activity, determined by DPPH assay. Similar to the previously discussed compound, the activity was due to the presence of a hydroxyl group in the aromatic core unit[67]. The antioxidant activity of the compound, 3-(3,4-dimethoxyphenyl)-1-(10-dodecyl phenothiazin-2-yl)prop-2-en-1-one **(61)** was evaluated using DPPH assay and found be having significant activity similar to the standard, ascorbic acid. The activity of this compound was due to the presence of the phenothiazine ring with its structure[68].

Anti-inflammatory activity of chalcones and their derivatives

A group of 2-methyl-4-phenyl quinoline-chalcone analogues **(62-64)** was designed and their anti-inflammatory potential was analysed. These potent compounds exhibited significant activity with better IC_{50} values and were also found to be having cyclooxygenase-2 inhibitory activity[25]. Chalcone derivative containing aryl-sulfonyl-piperazine fragment **(65)** was synthesized and evaluated its anti-inflammatory potential by using classical para-xylene-induced mice ear-swelling model and ELISA assays. It was found to be inhibiting the LPS-induced IL-6 and TNF-α release. The molecular docking studies also correlated with the *in vitro* and *in vivo* experimental results[69].

Conjugated indolyl chalcones **(66,67)** were afforded by the Knoevenagel condensation of 3- cyanoacetylindoles with substituted 3-chloro-3-phenyl-propenals. The anti-inflammatory effect of these compounds was evaluated against egg albumin denaturation and found to be highly effective in heat-induced albumin denaturation inhibition[70]. The antioxidant potential of (E)-1-(2-Hydroxyphenyl)-3-(3-ethoxy-4-hydroxyphenyl)prop-2-en-1-one **(68)** was evaluated against lipopolysaccharide-induced production of anti-inflammatory cytokines interleukin-6 inhibition and exhibited significant activity. The molecular docking results with the best binding affinity were also correlated with the experimental results[71].

Antidiabetic activity of chalcones and their derivatives

(E)-1-(2-Hydroxyphenyl)- 3-(2-Hydroxy-3-Methoxyphenyl) Prop-2-En-1-One **(69)** was synthesized by means of Claisen-Schmidt condensation and evaluated its potential against streptozocin induced diabetic mice. Postprandial hyperglycaemia along with blood glucose level was reduced significantly in a dose-dependent manner. The potent activity of this compound was due to the presence of electron-donating substituent in this structure[26]. (E)-1-(4′-Aminophenyl)-3-(3,5-dimethoxy,4-hydroxyphenyl) prop-2-en-1-one **(70)** and (E)-1-(4′-Aminophenyl)-3-(4-isopropyl phenyl) prop-2-en-1-one **(71)** were afforded by the reaction of 4-aminoacetophenone and aromatic aldehyde under microwave conditions at 180 W for 10-15 min. The antidiabetic potential of these compounds was tested using albino wrister rats and found to be exhibiting a significant effect by reducing blood glucose levels. The binding affinity of compounds with the diabetic targets also revealed the potent activity of these compounds, determined by molecular docking studies[72]. The antidiabetic potential of coumarin-chalcone hybrids, 4-(4-hydroxy-2-oxo-2H-chromen-8-yl)-6-methyl-5-(3-(3,4,5-trimethoxyphenyl) acryloyl)-3,4-dihydropyrimidin 2(1H)-one **(72)** and 4-hydroxy-8-(6-methyl-2-thioxo-5-(3-(3,4,5-trimethoxyphenyl) acryloyl)-1,2,3,4-tetrahydro pyrimidin4-yl)-2H-chromen-2-one **(73)** were determined by means of both *in vivo* and *in silico* studies. The *in silico* analysis of these compounds against the diabetic targets exhibited very low binding energy and showed better interactions. Based on the *in silico* molecular docking results, the *in vivo* studies were carried out and found to be exhibiting potent antidiabetic activity against streptozocin-induced diabetic animals with a significant reduction in blood glucose levels[73].

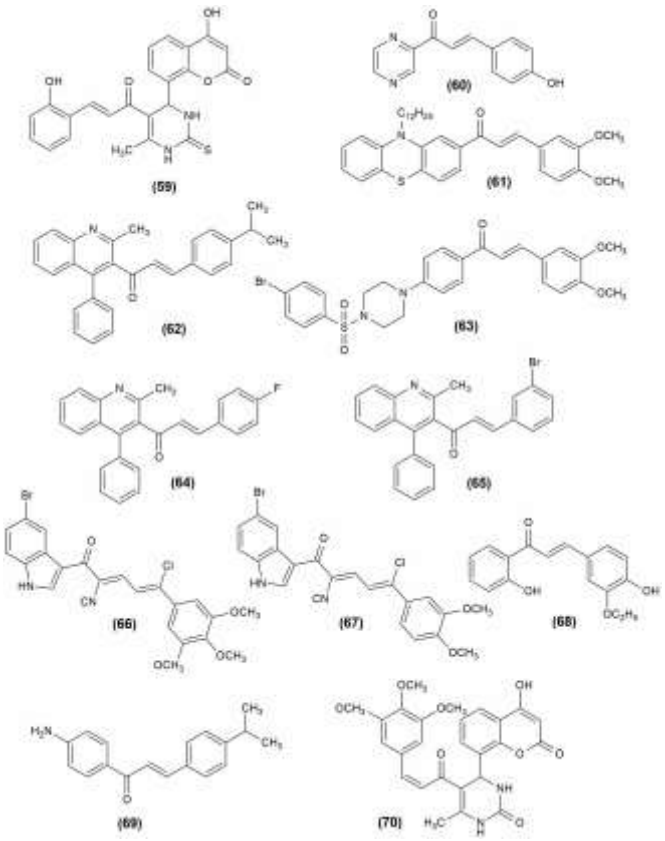

Figure 6: Compounds possessing antioxidant (59-61), anti-inflammatory (62-68) and antidiabetic (69-70) activities

Neurodegenerative activity of chalcones and their derivatives

The neurodegenerative activity of the chalcone analogue **(74)** synthesized from 7-methoxy-3,4-dihydronaphthalen1(2H)-one and aromatic aldehydes under basic conditions were evaluated and found to be the potent neuro-therapeutic compound against glutamate-induced cell death[23]. The acetylcholinesterase inhibitory activity of the novel chalcone namely, (E)-N-(4-(3-(pyridin-3-yl)acryloyl)phenyl)quinoline-3- carboxamide **(75)** was evaluated by using an Ellman's spectrophotometric method. The potent activity with a better IC_{50} value of this compound was due to the presence of the 3-pyridine group in its structure. The *in silico* studies were also correlated with the in vitro results, which exhibited better binding energy with better interactions[24]. μ-calpain and cathepsin β inhibitory activities (responsible for Alzheimer's disease) of various chalcones were evaluated by using a fluorometric m-calpain and cathepsin B assay. Among the various derivatives, the compounds (E)-1-(2,4-dihydroxy phenyl)-3-(4- hydroxynaphthalen-1-yl)prop-2-en-1-one **(76)** and (2E,4E)-5-(4-Hydroxy-3-methoxyphenyl)-1-(4- hydroxyl phenyl)penta-2,4-dien-1-one **(77)** were exhibited potent neuroprotective effect by inhibiting the enzymatic activities at the cellular level, followed by the p25 formation, tau

phosphorylation and insoluble Ab peptide formation reduction[74].

Quinoline containing chalcone derivatives **(78,79)** was designed and evaluated as cholinesterase inhibitors by using Ellman's spectrophotometric method. The *in vitro* results showed that these compounds exhibited better cholinesterase inhibitory activity with better IC_{50} values. The molecular docking results also revealed that these compounds had shown better binding affinity towards the cholinesterase targets and this was due to the presence of methyl and methoxy groups in side chain and dioxane ring in this structures[75]. The chalcone-triazole hybrids were synthesized and the neuroprotective potential was evaluated using SH-SY5Y cells. The compounds, (E)-3-(3,4-dimethoxyphenyl)-1-(4-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)phenyl)prop-2-en-1-one **(80)** and (E)-4-((1-(4-(3-(3,4-dimethoxyphenyl) acryloyl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde **(81)** were found to be having potent neurodegenerative potential, especially for Alzheimer's activity[76].

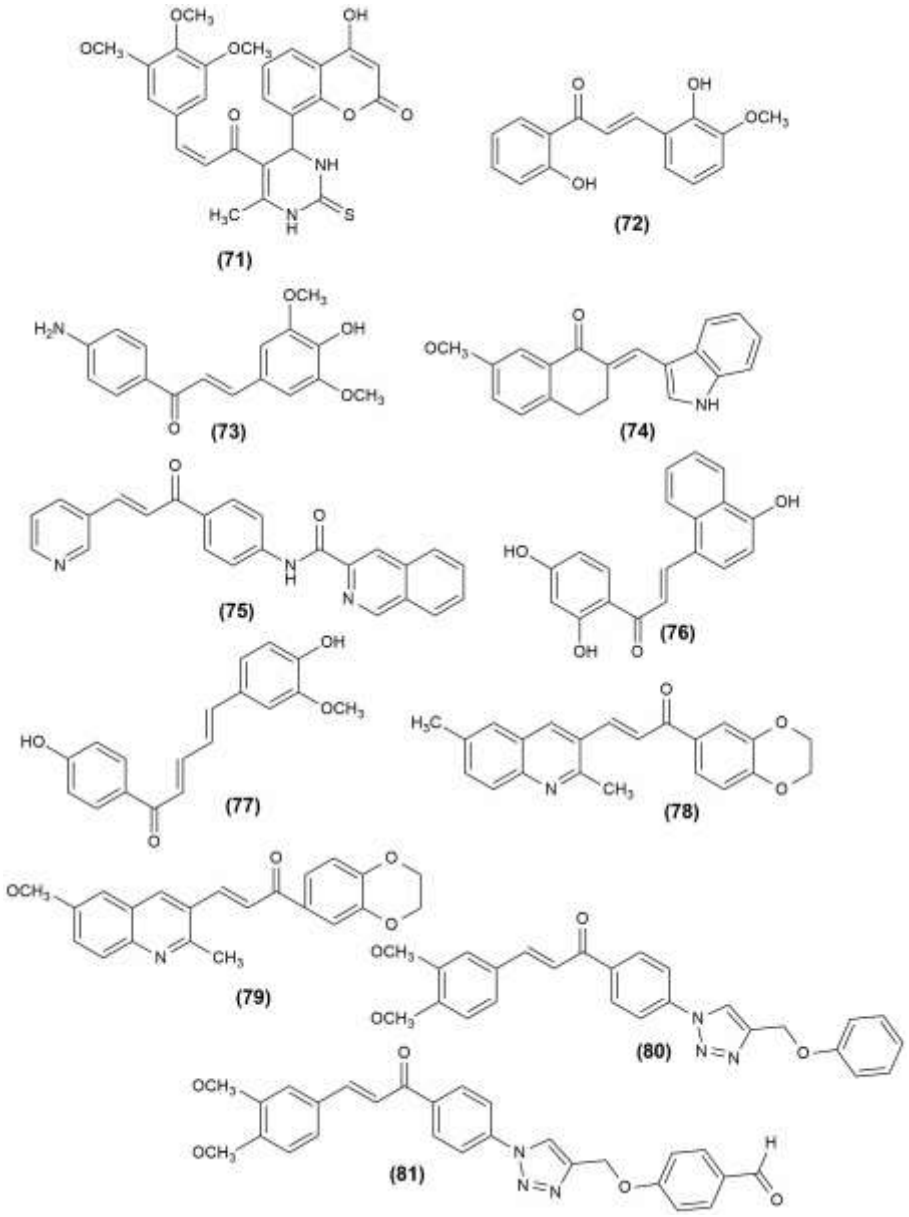

Figure 7: Compounds possessing antidiabetic (71-73) and neurodegenerative (74-81) activities

The anti-butyrylcholinesterase activity of the compound, (E)-3-(3-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butoxy)phenyl)-1-(2-hydroxyphenyl)pro p-2-en-1-one **(82)** was evaluated by using modified Ellman assay. This compound significantly inhibited self-induced and Cu^{2+}-induced Aβ1-42 aggregation. The exhibited results were found to be correlated with the molecular docking studies[77]. Chalcone-Vitamin E-donepezil hybrid, (E)-1-(3,6-dihydroxy-2,4-dimethoxyphenyl)-3-(4-((6-(ethyl(2- methoxybenzyl)amino)hexyl)oxy)phenyl)prop-2-en-1-one **(83)** was obtained by treating (E)-3-(4-(6-(ethyl(2-methoxybenzyl)amino)hexyloxy)- phenyl)-1-(6-hydroxy-2,4-dimethoxy-3-(methoxymethoxy)phenyl)prop-2-en-1-one with 10 % HCl and the anticholinesterase inhibitory activity of this compound was determined by using Ellman assay. This compound exhibited significant acetylcholinesterase inhibitory activity, along with the inhibition of self-induced and Cu^{2+}-induced Aβ1-42 aggregation. The molecular docking results also correlated with the experimental results, found to be a potent derivative for Alzheimer's disease[78].

Vitiligo treatment of chalcones and their derivatives

Novel isoxazole chalcone derivatives, 1-(4-((3-(3,4-Difluorophenyl)isoxazol-5-yl)methoxy) phenyl)-3-phenylprop-2-en-1-one **(84)** and 1-(4-((3-(2,3-Dihydrobenzo [b][1,4]dioxin-6-yl)isoxazol-5-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one **(85)** exhibited a stronger activity on melanogenesis and found to be the potent compounds for the treatment of vitiligo[27]. 2′,3,4, 4′-tetrahydrochalcone analogue **(86)** also exhibited better melanogenesis and was found to be a potent candidate for vitiligo treatment[79].

Antileishmanial activity of chalcones and their derivatives

The antileishmanial activity of chalcone derivative **(87)** was evaluated against *Leishmania infantum* promastigotes and found to be highly effective with better IC_{50} value. The molecular docking studies also correlated with this results[80]. The nitro-analogue, 3-nitro-2',4',6'- trimethoxychalcone **(88)** was found to be a potent broad-spectrum antileishmanial drug candidate, determined by the molecular modelling studies[81]. ((E)-1-(4,8-dimethoxynaphthalen-1-yl)-3-(4-nitrophenyl) prop-2-en-1-one) **(89)** was synthesized, evaluated and found to be effective against promastigote and amastigote forms of *L. amazonensis*. It was found to be a potent compound with a better IC_{50} value. The molecular docking studies also exhibited that the compound had more hydrogen bond interactions with the ARG enzyme and correlated with the experimental results[82]. Similarly, the antileishmanial activity of another chalcone derivative **(90)** was evaluated against *L. amazonensis* and was found to be exhibiting potent activity[83].

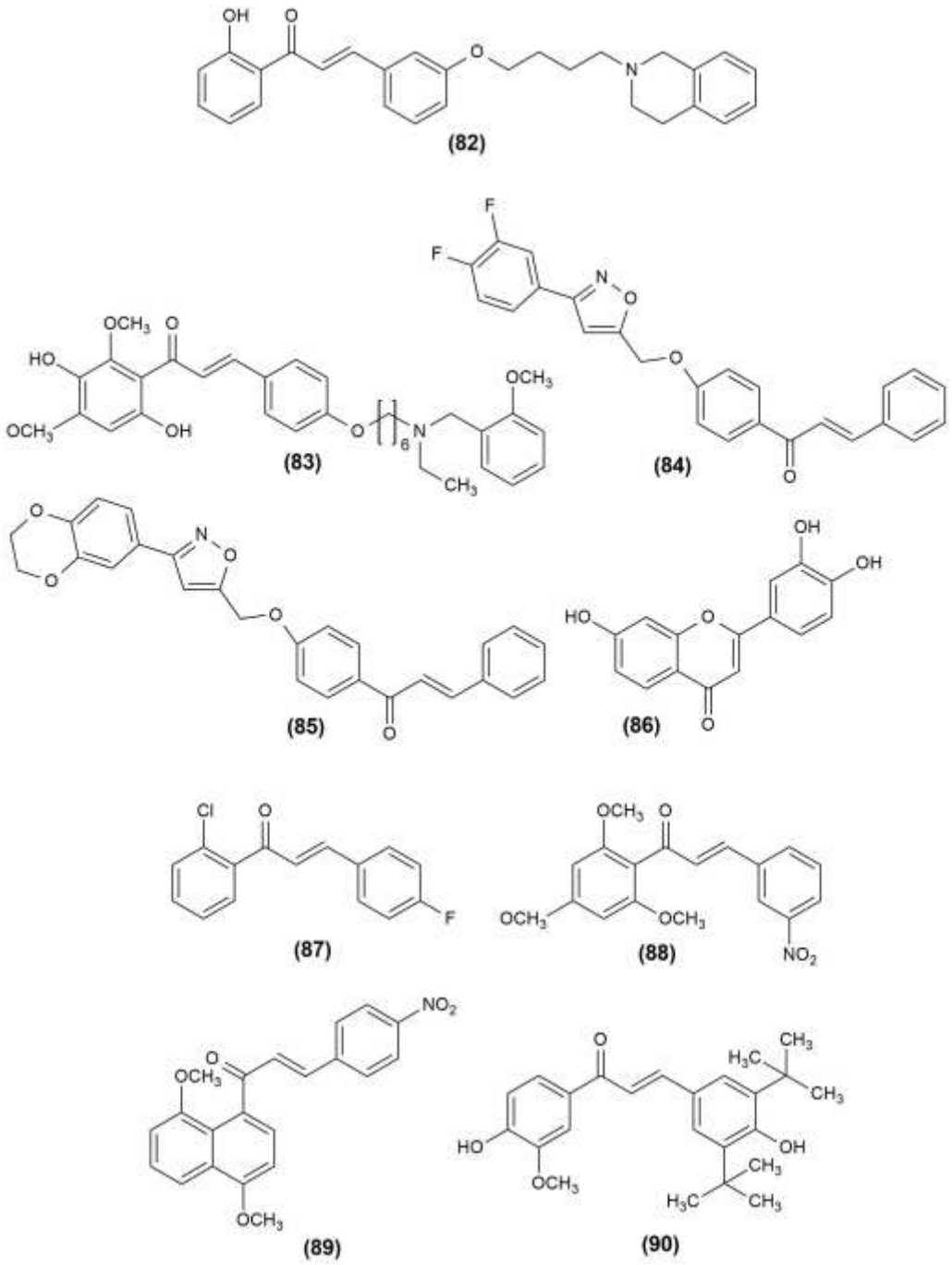

Figure 8: Compounds possessing neurogenerative (82-83), vitiligo treatment (84-86) and antileishmanial (87-90) activities

Conclusion

Being an important class of compounds in synthetic and pharmaceutical chemistry, the enormous biological application of chalcones and their derivatives are summarized in this review. The compounds possessing different biological applications including antimicrobial, anticancer, antimalarial, antitubercular, antioxidant, anti-inflammatory, antileishmanial, antidiabetic, neuroprotective, anti-Alzheimer, melanin formation and anti-vitiligo properties were discussed. These types of compounds were designed and synthesized by means of Claisen-Schmidt condensation, Knoevenagel condensation, crossed aldol condensation and Aldol condensation using microwave-assisted, ultrasonic-mediated and also by conventional synthetic approaches. Especially, these derivatives exhibit anticancer potential in a greater manner and found to act as tubulin polymerization inhibitors, microtubule-targeting agents, apoptosis inducers via various pathways, epidermal growth factor and vascular endothelial growth factor receptor inhibitors. Currently, these derivatives are widely designed and found to be possessing antimicrobial, anticancer and neuroprotective properties. These compounds also play a vital role in coordination chemistry and also in the development of chalcone-based hybrid molecules. Thus, by developing and implementing various greener mediated synthetic approaches, the novel derivatives of this moiety can be developed and tried for numerous applications in the future.

Acknowledgement

We thank the Management and Dr. G. Murugananthan, Principal of our college for giving constant support and encouragement for writing this review.

Authors Contributions: All the authors have contributed equally.

Funding: Nil.

Conflicts of Interests: The authors declare no conflict of interest.

References

1. Raju SK, Sekar P, Kumar S, Murugesan M, Karthikeyan, Arthanari M. Biological applications of imidazothiazole scaffolds: A current review. Journal of Advanced Chemical Sciences. 2022; 8(1):756-69. https://doi.org/10.30799/jacs.244.22080101

2. Kozłowska J, Potaniec B, Baczyńska D, Żarowska B, Anioł M. Synthesis and Biological Evaluation of Novel Aminochalcones as Potential Anticancer and Antimicrobial Agents. Molecules. 2019; 24(22):4129. https://doi.org/10.3390/molecules24224129

3. Rioux B, Pinon A, Gamond A, Martin F, Laurent A, Champavier Y, Barette C, Liagre B, Fagnère C, Sol V, Pouget C. Synthesis and biological evaluation of chalcone-polyamine conjugates as novel vectorized agents in colorectal and prostate cancer chemotherapy. European Journal of Medicinal Chemistry. 2021; 222:113586. https://doi.org/10.1016/j.ejmech.2021.113586

4. Lu CF, Wang SH, Pang XJ, Zhu T, Li HL, Li QR, Li QY, Gu YF, Mu ZY, Jin MJ, Li YR, Hu YY, Zhang YB, Song J, Zhang SY. Synthesis and Biological Evaluation of Amino Chalcone Derivatives as Antiproliferative Agents. Molecules. 2020; 25(23):5530. https://doi.org/10.3390/molecules25235530

5. Elkanzi NAA, Hrichi H, Alolayan RA, Derafa W, Zahou FM, Bakr RB. Synthesis of Chalcones Derivatives and Their Biological Activities: A Review. ACS Omega. 2022; 7(32):27769-27786. https://doi.org/10.1021/acsomega.2c01779

6. Gaonkar SL, Vignesh UN. Synthesis and pharmacological properties of chalcones: a review. Research on Chemistry Intermediates. 2017; 43:6043-6077. https://doi.org/10.1007/s11164-017-2977-5

7. Elshemy HAH, Zaki MA. Design and synthesis of new coumarin hybrids and insight into their mode of antiproliferative action. Bioorganic and Medicinal Chemistry. 2017; 25(3):1066-1075. https://doi.org/10.1016/j.bmc.2016.12.019

8. Bonakdar APS, Vafaei F, Farokhpour M, Esfahani M, Massah A. Synthesis and Anticancer Activity Assay of Novel Chalcone-Sulfonamide Derivatives. Iranian Journal of Pharmaceutical Research. 2017; 16:565-568.

9. Corsini E, Facchetti G, Esposito S, Maddalon A, Rimoldi I, Christodoulou MS. Antiproliferative effects of chalcones on T cell acute lymphoblastic leukemia-derived cells: Role of PKCβ. Archiv der Pharmazie. 2020; 353(7):e2000062. https://doi.org/10.1002/ardp.202000062

10. Peerzada MN, Khan P, Ahmad K, Hassan MI, Azam A. Synthesis, characterization and biological evaluation of tertiary sulfonamide derivatives of pyridyl-indole based heteroaryl chalcone as potential carbonic anhydrase IX inhibitors and anticancer agents. European Journal of Medicinal Chemistry. 2018; 155:13-23. https://doi.org/10.1016/j.ejmech.2018.05.034

11. Yadav DK, Kaushik P, Pankaj, Rana VS, Kamil D, Khatri D, Shakil NA. Microwave Assisted Synthesis, Characterization and Biological Activities of Ferrocenyl Chalcones and Their QSAR Analysis. Frontiers in Chemistry. 2019; 7:814. https://doi.org/10.3389/fchem.2019.00814

12. Homerin G, Nica AS, Farce A, Dubois J, Ghinet A. Ultrasounds-mediated 10-seconds synthesis of chalcones as potential farnesyltransferase inhibitors. Bioorganic and Medicinal Chemistry Letters. 2020; 30(11):127149. https://doi.org/10.1016/j.bmcl.2020.127149

13. Blanco Z, Fernandez-Moreira E, Mijares MR, Celis C, Martínez G, De Sanctis JB, Gurská S, Džubák P, Hajdůch M, Mijoba A, García Y, Serrano X, Herrera N, Correa-Abril J, Parra Y, Ángel J, Ramírez H, Charris JE. Synthesis, Leishmanicidal, Trypanocidal, Antiproliferative Assay and Apoptotic Induction of (2-Phenoxypyridin-3-yl)naphthalene-1(2H)-one Derivatives. Molecules. 2022; 27(17):5626. https://doi.org/10.3390/molecules27175626

14. Zhou W, Zhang W, Peng Y, Jiang ZH, Zhang L, Du Z. Design, Synthesis and Anti-Tumor Activity of Novel Benzimidazole-Chalcone Hybrids as Non-Intercalative Topoisomerase II Catalytic Inhibitors. Molecules. 2020; 25(14):3180. https://doi.org/10.3390/molecules25143180

15. Preti D, Romagnoli R, Rondanin R, Cacciari B, Hamel E, Balzarini J, Liekens S, Schols D, Estévez-Sarmiento F, Quintana J, Estévez F. Design, synthesis, in vitro antiproliferative activity and apoptosis-inducing studies of 1-(3',4',5'-trimethoxyphenyl)-3-(2'-alkoxycarbonylindolyl)-2-propen-1-one derivatives obtained by a molecular hybridisation approach. Journal of Enzyme Inhibition and Medicinal Chemistry. 2018; 33(1):1225-1238. https://doi.org/10.1080/14756366.2018.1493473

16. Sultana F, Reddy Bonam S, Reddy VG, Nayak VL, Akunuri R, Rani Routhu S, Alarifi A, Halmuthur MSK, Kamal A. Synthesis of benzo[d]imidazo[2,1-b]thiazole-chalcone conjugates as microtubule targeting and apoptosis inducing agents. Bioorganic Chemistry. 2018; 76:1-12. https://doi.org/10.1016/j.bioorg.2017.10.019

17. Pereira D, Durães F, Szemerédi N, Freitas-da-Silva J, Pinto E, Martins-da-Costa P, Pinto M, Correia-da-Silva M, Spengler G, Sousa E, Cidade H. New Chalcone-Triazole Hybrids with Promising Antimicrobial Activity in Multidrug Resistance Strains. International Journal of Molecular Science. 2022; 23(22):14291. https://doi.org/10.3390/ijms232214291

18. Castaño LF, Quiroga J, Abonia R, Insuasty D, Vidal OM, Seña R, Rubio V, Puerto G, Nogueras M, Cobo J, Guzman J, Insuasty A, Insuasty B. Synthesis, Anticancer and Antitubercular Properties of New Chalcones and Their Nitrogen-Containing Five-Membered Heterocyclic Hybrids Bearing Sulfonamide Moiety. International

Journal of Molecular Science. 2022; 23(20):12589. https://doi.org/10.3390/ijms232012589

19. Li X, Chen B, Xie H, He Y, Zhong D, Chen D. Antioxidant Structure-Activity Relationship Analysis of Five Dihydrochalcones. Molecules. 2018; 23(5):1162. https://doi.org/10.3390/molecules23051162

20. Mahapatra DK, Bharti SK, Asati V. Chalcone Derivatives: Anti-inflammatory Potential and Molecular Targets Perspectives. Current Topics in Medicinal Chemistry. 2017 N; 17(28):3146-3169. https://doi.org/10.2174/1568026617666170914160446

21. Kuttithodi AM, Nikhitha D, Jacob J, Narayanankutty A, Mathews M, Olatunji OJ, Rajagopal R, Alfarhan A, Barcelo D. Antioxidant, Antimicrobial, Cytotoxicity, and Larvicidal Activities of Selected Synthetic Bis-Chalcones. Molecules. 2022; 27(23):8209. https://doi.org/10.3390/molecules27238209

22. Singh A, Rani A, Gut J, Rosenthal PJ, Kumar V. Piperazine-linked 4-aminoquinoline-chalcone/ferrocenyl-chalcone conjugates: Synthesis and antiplasmodial evaluation. Chemical Biology and Drug Design. 2017; 90(4):590-595. https://doi.org/10.1111/cbdd.12982

23. Selvaraj B, Nguyen UTT, Huh G, Nguyen DH, Mok IK, Lee H, Kang K, Bae AN, Kim DW, Lee JW. Synthesis and biological evaluation of chalcone derivatives as neuroprotective agents against glutamate-induced HT22 mouse hippocampal neuronal cell death. Bioorganic and Medicinal Chemistry Letters. 2020; 30(22):127597. https://doi.org/10.1016/j.bmcl.2020.127597

24. Polo E, Ibarra-Arellano N, Prent-Peñaloza L, Morales-Bayuelo A, Henao J, Galdámez A, Gutiérrez M. Ultrasound-assisted synthesis of novel chalcone, heterochalcone and bis-chalcone derivatives and the evaluation of their antioxidant properties and as acetylcholinesterase inhibitors. Bioorganic Chemistry. 2019; 90:103034. https://doi.org/10.1016/j.bioorg.2019.103034

25. Huang ZH, Yin LQ, Guan LP, Li ZH, Tan C. Screening of chalcone analogs with anti-depressant, anti-inflammatory, analgesic, and COX-2-inhibiting effects. Bioorganic and Medicinal Chemistry Letters. 2020; 30(11):127173. https://doi.org/10.1016/j.bmcl.2020.127173

26. Welday Kahssay S, Hailu GS, Taye Desta K. Design, Synthesis, Characterization and in vivo Antidiabetic Activity Evaluation of Some Chalcone Derivatives. Drug Design, Development and Therapy. 2021; 15:3119-3129. https://doi.org/10.2147/DDDT.S316185

27. Niu C, Yin L, Nie LF, Dou J, Zhao JY, Li G, Aisa HA. Synthesis and bioactivity of novel isoxazole chalcone derivatives on tyrosinase and melanin synthesis in murine B16 cells for the treatment of vitiligo. Bioorganic and Medicinal Chemistry. 2016; 24(21):5440-5448. https://doi.org/10.1016/j.bmc.2016.08.066

28. Scherbakov AM, Zavarzin IV, Vorontsova SK, Hajra A, Andreeva OE, Yadykov AV, Levina IS, Volkova YA, Shirinian VZ. Synthesis and evaluation of the antiproliferative activity of benzylidenes of 16-dehydroprogesterone series. Steroids. 2018; 138:91-101. https://doi.org/10.1016/j.steroids.2018.06.013

29. Zhu H, Tang L, Zhang C, Wei B, Yang P, He D, Zheng L, Zhang Y. Synthesis of Chalcone Derivatives: Inducing Apoptosis of HepG2 Cells via Regulating Reactive Oxygen Species and Mitochondrial Pathway. Frontiers in Pharmacology. 2019; 10:1341. doi: 10.3389/fphar.2019.01341.

https://doi.org/10.3389/fphar.2019.01341

30. Garcia MAR, Theodoro RS, Sardi JCO, Santos MB, Ayusso GM, Pavan FR, Costa AR, Santa Cruz LM, Rosalen PL, Regasini LO. Design, synthesis and antibacterial activity of chalcones against MSSA and MRSA planktonic cells and biofilms. Bioorganic Chemistry. 2021; 116:105279. https://doi.org/10.1016/j.bioorg.2021.105279

31. Bala D, Jinga LI, Popa M, Hanganu A, Voicescu M, Bleotu C, Tarko L, Nica S. Design, Synthesis, and Biological Evaluation of New Azulene-Containing Chalcones. Materials (Basel). 2022; 15(5):1629. https://doi.org/10.3390/ma15051629

32. Illicachi LA, Montalvo-Acosta JJ, Insuasty A, Quiroga J, Abonia R, Sortino M, Zacchino S, Insuasty B. Synthesis and DFT Calculations of Novel Vanillin-Chalcones and Their 3-Aryl-5-(4-(2-(dimethylamino)-ethoxy)-3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde Derivatives as Antifungal Agents. Molecules. 2017; 22(9):1476. https://doi.org/10.3390/molecules22091476

33. Mellado M, Espinoza L, Madrid A, Mella J, Chávez-Weisser E, Diaz K, Cuellar M. Design, synthesis, antifungal activity, and structure-activity relationship studies of chalcones and hybrid dihydrochromane-chalcones. Molecular Diversity. 2020; 24:603-615. https://doi.org/10.1007/s11030-019-09967-y

34. Siqueira MMR, Freire PTC, Cruz BG, de Freitas TS, Bandeira PN, Silva Dos Santos H, Nogueira CES, Teixeira AMR, Pereira RLS, Xavier JDC, Campina FF, Dos Santos Barbosa CR, Neto JBA, da Silva MMC, Siqueira-Júnior JP, Douglas Melo Coutinho H. Aminophenyl chalcones potentiating antibiotic activity and inhibiting bacterial efflux pump. European Journal of Pharmaceutical Sciences. 2021; 158:105695. https://doi.org/10.1016/j.ejps.2020.105695

35. Yadav P, Lal K, Kumar L, Kumar A, Kumar A, Paul AK, Kumar R. Synthesis, crystal structure and antimicrobial potential of some fluorinated chalcone-1,2,3-triazole conjugates. European Journal of Medicinal Chemistry. 2018; 155:263-274. https://doi.org/10.1016/j.ejmech.2018.05.055

36. Burmaoglu S, Algul O, Gobek A, Aktas Anil D, Ulger M, Erturk BG, Kaplan E, Dogen A, Aslan G. Design of potent fluoro-substituted chalcones as antimicrobial agents. Journal of Enzyme Inhibition and Medicinal Chemistry. 2017; 32(1):490-495. https://doi.org/10.1080/14756366.2016.1265517

37. Alrohily WD, Habib ME, El-Messery SM, Alqurshi A, El-Subbagh H, Habib EE. Antibacterial, antibiofilm and molecular modeling study of some antitumor thiazole based chalcones as a new class of DHFR inhibitors. Microbial Pathogenesis. 2019; 136:103674. https://doi.org/10.1016/j.micpath.2019.103674

38. Kumar G, Siva Krishna V, Sriram D, Jachak SM. Pyrazole-coumarin and pyrazole-quinoline chalcones as potential antitubercular agents. Archive der Pharmazie. 2020; 353(8):e2000077. https://doi.org/10.1002/ardp.202000077

39. Singh A, Biot C, Viljoen A, Dupont C, Kremer L, Kumar K, Kumar V. 1H-1,2,3-triazole-tethered uracil-ferrocene and uracil-ferrocenylchalcone conjugates: Synthesis and antitubercular evaluation. Chemical Biology and Drug Design. 2017; 89(6):856-861.https://doi.org/10.1111/cbdd.12908

40. Gomes MN, Braga RC, Grzelak EM, Neves BJ, Muratov E, Ma R, Klein LL, Cho S, Oliveira GR, Franzblau SG, Andrade CH. QSAR-driven design, synthesis and discovery of potent chalcone derivatives with antitubercular activity. European Journal of Medicinal Chemistry. 2017; 137:126-138. https://doi.org/10.1016/j.ejmech.2017.05.026

41. Sahoo SK, Rani B, Gaikwad NB, Ahmad MN, Kaul G, Shukla M, Nanduri S, Dasgupta A, Chopra S, Yaddanapudi VM. Synthesis and structure-activity relationship of new chalcone linked 5-phenyl-3-isoxazolecarboxylic acid methyl esters potentially active against drug resistant Mycobacterium tuberculosis. European Journal of Medicinal Chemistry. 2021; 222:113580. https://doi.org/10.1016/j.ejmech.2021.113580

42. Hameed, A., Masood, S., Hameed, A, Ahmed E, Sharif A, Abdullah MI. Anti-malarial, cytotoxicity and molecular docking studies of quinolinyl chalcones as potential anti-malarial agent. Journal of Computer-Aided Molecular Design. 2019; 33:677-688. https://doi.org/10.1007/s10822-019-00210-2

43. Jufrizal Syahri, Emmy Yuanita, Beta Achromi Nurohmah, Ria Armunanto, Bambang Purwono. Chalcone analogue as potent anti-malarial compounds against Plasmodium falciparum: Synthesis, biological evaluation, and docking simulation study. Asian Pacific Journal of Tropical Biomedicine. 2017; 7(8):675-679. https://doi.org/10.1016/j.apjtb.2017.07.004

44. Syahri J, Nasution H, Nurohmah BA, Purwono B, Yuanita E. Aminoalkylated chalcone: Synthesis, biological evaluation, and docking simulation as potent antimalarial agents. Journal of

Applied Pharmaceutical Science. 2020; 10(06):001-005. https://doi.org/10.7324/JAPS.2020.10601

45. Jyoti, Gaur R, Kumar Y, Cheema HS, Kapkoti DS, Darokar MP, Khan F, Bhakuni RS. Synthesis, molecular modelling studies of indolyl chalcone derivatives and their antimalarial activity evaluation. Natural Product Research. 2021; 35(19):3261-3268. https://doi.org/10.1080/14786419.2019.1696788

46. Nitin H. Andhare, Mohammad Anas, Sumit K. Rastogi et al. Synthesis and in vitro SAR evaluation of natural vanillin-based chalcones tethered quinolines as antiplasmodial agents, Medicinal Chemistry Research. 2022. https://doi.org/10.21203/rs.3.rs-1522845/v1

47. Sinha S, Batovska DI, Medhi B, Radotra BD, Bhalla A, Markova N, Sehgal R. In vitro anti-malarial efficacy of chalcones: cytotoxicity profile, mechanism of action and their effect on erythrocytes. Malarian Journal. 2019; 18. https://doi.org/10.1186/s12936-019-3060-z

48. Wang G, Qiu J, Xiao X, Cao A, Zhou F. Synthesis, biological evaluation and molecular docking studies of a new series of chalcones containing naphthalene moiety as anticancer agents. Bioorganic Chemistry. 2018; 76:249-257. https://doi.org/10.1016/j.bioorg.2017.11.017

49. Wang G, Liu W, Gong Z, Huang Y, Li Y, Peng Z. Synthesis, biological evaluation, and molecular modelling of new naphthalene-chalcone derivatives as potential anticancer agents on MCF-7 breast cancer cells by targeting tubulin colchicine binding site. Journal of Enzyme Inhibition and Medicinal Chemistry. 2020; 35(1):139-144. https://doi.org/10.1080/14756366.2019.1690479

50. Wang G, Peng Z, Li Y. Synthesis, Anticancer Activity and Molecular Modeling Studies of Novel Chalcone Derivatives Containing Indole and Naphthalene Moieties as Tubulin Polymerization Inhibitors. Chemical and Pharmaceutical Bulletin (Tokyo). 2019; 67(7):725-728. https://doi.org/10.1248/cpb.c19-00217

51. Wang FC, Peng B, Cao SL, Li HY, Yuan XL, Zhang TT, Shi R, Li Z, Liao J, Wang H, Li J, Xu X. Synthesis and cytotoxic activity of chalcone analogues containing a thieno[2,3-d]pyrimidin-2-yl group as the A-ring or B-ring. Bioorganic Chemistry. 2020; 94:103346. https://doi.org/10.1016/j.bioorg.2019.103346

52. Saavedra E, Del Rosario H, Brouard I, Quintana J, Estévez F. 6'-Benzyloxy-4-bromo-2'-hydroxychalcone is cytotoxic against human leukaemia cells and induces caspase-8- and reactive oxygen species-dependent apoptosis. Chemical Biology Interactions. 2019; 298:137-145. https://doi.org/10.1016/j.cbi.2018.12.010

53. Ayati A, Esmaeili R, Moghimi S, Oghabi Bakhshaiesh T, Eslami-S Z, Majidzadeh-A K, Safavi M, Emami S, Foroumadi A. Synthesis and biological evaluation of 4-amino-5-cinnamoylthiazoles as chalcone-like anticancer agents. European Journal of Medicinal Chemistry. 2018; 145:404-412. https://doi.org/10.1016/j.ejmech.2018.01.015

54. Dong J, Yang J, Yu W, Li H, Cai M, Xu JL, Xu HD, Shi YF, Guan X, Cheng XD, Qin JJ. Discovery of benzochalcone derivative as a potential antigastric cancer agent targeting signal transducer and activator of transcription 3 (STAT3). Journal of Enzyme Inhibition and Medicnal Chemistry. 2022; 37(1):2004-2016. https://doi.org/10.1080/14756366.2022.2100366

55. Halim PA, Hassan RA, Mohamed KO, Hassanin SO, Khalil MG, Abdou AM, Osman EO. Synthesis and biological evaluation of halogenated phenoxychalcones and their corresponding pyrazolines as cytotoxic agents in human breast cancer. Journal of Enzyme Inhibition and Medicinal Chemistry. 2022; 37(1):189-201. https://doi.org/10.1080/14756366.2021.1998023

56. Farghaly TA, Masaret GS, Muhammad ZA, Harras MF. Discovery of thiazole-based-chalcones and 4-hetarylthiazoles as potent anticancer agents: Synthesis, docking study and anticancer activity. Bioorganic Chemistry. 2020; 98:103761. https://doi.org/10.1016/j.bioorg.2020.103761

57. Durgapal SD, Soni R, Umar S, Suresh B, Soman SS. 3-Aminomethyl pyridine chalcone derivatives: Design, synthesis, DNA binding and cytotoxic studies. Chemical Biology and Drug Design. 2018; 92(1):1279-1287. https://doi.org/10.1111/cbdd.13189

58. Burmaoglu S, Ozcan S, Balcioglu S, Gencel M, Noma SAA, Essiz S, Ates B, Algul O. Synthesis, biological evaluation and molecular docking studies of bis-chalcone derivatives as xanthine oxidase inhibitors and anticancer agents. Bioorganic Chemistry. 2019; 91:103149. https://doi.org/10.1016/j.bioorg.2019.103149

59. Zhang SY, Fu DJ, Yue XX, Liu YC, Song J, Sun HH, Liu HM, Zhang YB. Design, Synthesis and Structure-Activity Relationships of Novel Chalcone-1,2,3-triazole-azole Derivates as Antiproliferative Agents. Molecules. 2016; 21(5):653. https://doi.org/10.3390/molecules21050653

60. Luo Y, Wu W, Zha D, Zhou W, Wang C, Huang J, Chen S, Yu L, Li Y, Huang Q, Zhang J, Zhang C. Synthesis and biological evaluation of novel ligustrazine-chalcone derivatives as potential anti-triple negative breast cancer agents. Bioorganic and Medicinal Chemistry Letters. 2021; 47:128230. https://doi.org/10.1016/j.bmcl.2021.128230

61. Madhavi S, Sreenivasulu R, Yazala JP, Raju RR. Synthesis of chalcone incorporated quinazoline derivatives as anticancer agents. Saudi Pharmaceutical Journal. 2017; 25(2):275-279. https://doi.org/10.1016/j.jsps.2016.06.005

62. Padhy GK, Rath D, Bhukta P, Kumar LA, Sethy K, Panda J, Raul SK, Behera AK. Synthesis Of Novel Benzimidazole-Pyrazoline Hybrid Molecules as Antibacterial and Anticancer Agent. Journal of Pharmaceutical Negative Results. 2023; 14(1):521-26. doi: 10.47750/pnr.2023.14.S01.61

63. John A, Ebune A, Aderemi I, Moyosore A, Idah G. Theoretical Investigation and Design of Novel Anti-proliferative Agents against Hepatocellular Carcinoma from Benzimidazole-Chalcone derivatives. Advanced Journal of Chemistry-Section A, 2023:92-104. https://doi.org/10.22034/ajca.2023.365669.1336

64. Osmaniye D, Sağlık BN, Khalilova N, Levent S, Bayazıt G, Gül UD, Zkay YO, Kaplancıklı ZA. Design, Synthesis, and Biological Evaluation Studies of Novel Naphthalene-Chalcone Hybrids As Antimicrobial, Anticandidal, Anticancer, and VEGFR 2 Inhibitors. ACS Omega. 2023; 8(7):6669-6678. https://doi.org/10.1021/acsomega.2c07256

65. Guazelli CFS, Fattori V, Ferraz CR, Borghi SM, Casagrande R, Baracat MM, Verri WA Jr. Antioxidant and anti-inflammatory effects of hesperidin methyl chalcone in experimental ulcerative colitis. Chemical Biology Interactions. 2021; 333:109315. https://doi.org/10.1016/j.cbi.2020.109315

66. Konidala SK, Kotra V, Danduga RCSR, Kola PK, Bhandare RR, Shaik AB. Design, multistep synthesis and in-vitro antimicrobial and antioxidant screening of coumarin clubbed chalcone hybrids through molecular hybridization approach. Arabian Journal of Chemistry. 2021; 14(6):1878-5352. https://doi.org/10.1016/j.arabjc.2021.103154

67. Stepanić V, Matijašić M, Horvat T, Verbanac D, Kučerová-Chlupáčová M, Saso L, Žarković N. Antioxidant Activities of Alkyl Substituted Pyrazine Derivatives of Chalcones-In Vitro and In Silico Study. Antioxidants. 2019; 8(4):90. https://doi.org/10.3390/antiox8040090

68. Al Zahrani NA, El-Shishtawy RM, Elaasser MM, Asiri AM. Synthesis of Novel Chalcone-Based Phenothiazine Derivatives as Antioxidant and Anticancer Agents. Molecules. 2020; 25(19):4566. https://doi.org/10.3390/molecules25194566

69. Li J, Li D, Xu Y, Guo Z, Liu X, Yang H, Wu L, Wang L. Design, synthesis, biological evaluation, and molecular docking of chalcone derivatives as anti-inflammatory agents. Bioorganic and Medicinal Chemistry Letters. 2017; 27(3):602-606. https://doi.org/10.1016/j.bmcl.2016.12.008

70. Bhale PS, Chavan HV, Dongare SB, Shringare SN, Mule YB, Nagane SS, Bandgar BP. Synthesis of extended conjugated indolyl chalcones as potent anti-breast cancer, anti-inflammatory and antioxidant agents. Bioorganic and Medicinal Chemistry Letters. 2017; 27(7):1502-1507. https://doi.org/10.1016/j.bmcl.2017.02.052

71. Nurkenov OA, Ibraev MK, Schepetkin IA, Khlebnikov AI, Seilkhanov TM, Arinova AE, Isabaeva MB. Synthesis, Structure, and Anti-Inflammatory Activity of Functionally Substituted Chalcones and Their Derivatives. Russian Journal of General Chemistry. 2019; 89:1360-1367. https://doi.org/10.1134/S1070363219070028

72. Rammohan A, Bhaskar BV, Venkateswarlu N, Gu W, Zyryanov GV. Design, synthesis, docking and biological evaluation of chalcones as promising antidiabetic agents. Bioorganic Chemistry. 2020; 95:103527. https://doi.org/10.1016/j.bioorg.2019.103527

73. Konidala SK, Kotra V, Danduga RCSR, Kola PK. Coumarin-chalcone hybrids targeting insulin receptor: Design, synthesis, anti-diabetic activity, and molecular docking. Bioorganic Chemistry. 2020; 104:104207. https://doi.org/10.1016/j.bioorg.2020.104207

74. Jeon KH, Lee E, Jun KY, Eom JE, Kwak SY, Na Y, Kwon Y. Neuroprotective effect of synthetic chalcone derivatives as competitive dual inhibitors against μ-calpain and cathepsin B through the downregulation of tau phosphorylation and insoluble Aβ peptide formation. European Journal of Medicinal Chemistry. 2016; 121:433-444. https://doi.org/10.1016/j.ejmech.2016.06.008

75. Shah MS, Najam-Ul-Haq M, Shah HS, Farooq Rizvi SU, Iqbal J. Quinoline containing chalcone derivatives as cholinesterase inhibitors and their in silico modeling studies. Computational Biology and Chemistry. 2018; 76:310-317. doi: 10.1016/j.compbiolchem.2018.08.003.

https://doi.org/10.1016/j.compbiolchem.2018.08.003

76. Sooknual P, Pingaew R, Phopin K, Ruankham W, Prachayasittikul S, Ruchirawat S, Prachayasittikul V. Synthesis and neuroprotective effects of novel chalcone-triazole hybrids. Bioorganic Chemistry. 2020; 105:104384. https://doi.org/10.1016/j.bioorg.2020.104384

77. Sang Z, Wang K, Zhang P, Shi J, Liu W, Tan Z. Design, synthesis, in-silico and biological evaluation of novel chalcone derivatives as multi-function agents for the treatment of Alzheimer's disease. European Journal of Medicinal Chemistry. 2019; 180:238-252. https://doi.org/10.1016/j.ejmech.2019.07.021

78. Sang Z, Song Q, Cao Z, Deng Y, Zhang L. Design, synthesis, and evaluation of chalcone-Vitamin E-donepezil hybrids as multi-target-directed ligands for the treatment of Alzheimer's disease. Journal of Enzyme Inhibition and Medicinal Chemistry. 2022; 37(1):69-85. https://doi.org/10.1080/14756366.2021.1993845

79. Zhong H, Zhou J, An XH, Hua YR, Lai YF, Zhang R, Ahmad O, Zhang Y, Shang J. Natural product-based design, synthesis and biological evaluation of 2',3,4,4'-tetrahydrochalcone analogues as antivitiligo agents. Bioorganic Chemistry. 2019; 87:523-533. https://doi.org/10.1016/j.bioorg.2019.03.054

80. Garcia AR, Oliveira DMP, Jesus JB, Souza AMT, Sodero ACR, Vermelho AB, Leal ICR, Souza ROMA, Miranda LSM, Pinheiro AS, Rodrigues IA. Identification of Chalcone Derivatives as Inhibitors of Leishmania infantum Arginase and Promising Antileishmanial Agents. Frontiers in Chemistry. 2021; 8:624678. https://doi.org/10.3389/fchem.2020.624678

81. Escrivani DO, Charlton RL, Caruso MB, Burle-Caldas GA, Borsodi MPG, Zingali RB, Arruda-Costa N, Palmeira-Mello MV, de Jesus JB, Souza AMT, Abrahim-Vieira B, Freitag-Pohl S, Pohl E, Denny PW, Rossi-Bergmann B, Steel PG. Chalcones identify cTXNPx as a potential antileishmanial drug target. PLOS Neglected Tropical Diseases. 2021; 15(11):e0009951. https://doi.org/10.1371/journal.pntd.0009951

82. de Santiago-Silva KM, Bortoleti BTDS, Oliveira LDN, Maia FLA, Castro JC, Costa IC, Lazarin DB, Wardell JL, Wardell SMSV, Albuquerque MG, Lima CHDS, Pavanelli WR, Bispo MLF, Gonçalves RSB. Antileishmanial Activity of 4,8-Dimethoxynaphthalenyl Chalcones on Leishmania amazonensis. Antibiotics. 2022; 11(10):1402. https://doi.org/10.3390/antibiotics11101402

83. Alonso L, Menegatti R, Gomes RS, Dorta ML, Luzin RM, Lião LM, Alonso A. Antileishmanial activity of the chalcone derivative LQFM064 associated with reduced fluidity in the parasite membrane as assessed by EPR spectroscopy. European Journal of Pharmaceutical Sciences. 2020; 151:105407. https://doi.org/10.1016/j.ejps.2020.105407